REMARKS

Claims 27, 28, 31 and 40-42 are currently pending with claims 27 being independent. Claim 31 is currently amended to correct a typographical error. No new matter has been added.

Claim Rejections – 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 31 and 40-42 under 35 U.S.C. § 112, second paragraph, as indefinite. Specifically, the Examiner alleges that claim 31 recites the phrase "vascular epithelial growth factor ("VEGF"), but there is no particular definition of the term in the specification and it does not appear to be recognized in the art. The recitation of "epithelial" instead of "endothelial" in claim 31 and in the specification on pages 13 and 14 was the result of a typographical error. The Applicants intended to refer to vascular endothelial growth factor as evidenced by the use of the art recognized acronym "VEGF" following each instance of the term on pages 13 and 14. VEGF was recognized in the art as the acronym for vascular endothelial growth factor. See attached Exhibit A. Accordingly the specification and claim 31 have been amended to correct the typographical error and recite vascular endothelial growth factor, thereby obviating the rejection. Accordingly, Applicant's respectfully request that the rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103(a)

The Examiner rejected claim 27 under 35 U.S.C. § 103(a) as being unpatentable over Fitzgerald *et al.* 32 Cell 607 (1983), hereinafter "Fitzgerald." in view of Leizer *et al.* 76 Blood 1989 (1990), hereinafter "Leizer." The Examiner alleges that Fitzgerald teaches the use of a composition comprising adenovirus and EGF bound to colloidal gold. *Office Action* at ¶ 9. The Examiner notes Fitzgerald does not teach that EGF is a cytokine, but relies on Leitzer as establishing that EGF is a cytokine. *Id.* The Examiner alleges that Fitzgerald teaches that adenovirus enters the cell via internalization by a receptor-mediated process thereby qualifying as a "targeting molecule" as defined in the specification. *Id.* at ¶ 10. The Examiner also alleges that Fitzgerald teaches that EGF can be conjugated with *Pseudomonas* exotoxin, and that when

using the "colloidal gold complex" PE-EGF toxicity in KB tumor cells is enhanced. *Id.* at ¶ 9. The Examiner acknowledges that Fitzgerald does not teach administration of colloidal gold to a human or animal. *Id.* at ¶ 12. However, the Examiner alleges that Fitzgerald teaches that the compositions utilized by Fitzgerald are useful for delivering materials into cells. *Id.* at ¶ 13. Therefore, the Examiner alleges it would have been obvious to one of ordinary skill in the art to use the method taught by Fitzgerald in a human or animal with a reasonable expectation of success. *Id.* at ¶ 14. The Applicants respectfully traverse this rejection

Fitzgerald does not teach the use of a colloidal gold complex comprising a cytokine (EGF) and a target molecule (adenovirus), or a colloidal gold complex comprising PE-EGF as asserted by the Examiner. As the Examiner is aware, when reading a peer-reviewed scientific journal all disclosure in the "Abstract," "Results," and "Discussion" sections of the paper refer back to the experiments as defined in the "Experimental Procedures" section. Therefore, to understand the actual compositions and methods used by Fitzgerald it is necessary to carefully review the "Experimental Procedures" section on pages 615-616. Upon such a review, it is clear Fitzgerald does not teach the use of a single composition comprising EGF or PE-EGF and adenovirus bound to colloidal gold.

The Examiner cites to page 613 of Fitzgerald, claiming Fitzgerald teaches enhanced PE-EGF toxicity when bound to a colloidal gold complex. Turning to the Experimental Procedures section, it is clear these experiments did not involve a PE-EGF, adenovirus, colloidal gold complex. Adenovirus and PE-EGF were administered separately and in the complete absence of colloidal gold. "Adenovirus … was allowed to bind to cells during a 2 hr incubation at 4° C, the cells were washed and either PE … or PE-EGF was added. *Id.* at 616, first column, second full paragraph. Accordingly, Fitzgerald is silent as to any enhancement of PE-EGF toxicity by binding to colloidal gold, and the Examiner's assertions to this point are moot.

The Examiner also cites to the "Abstract." The abstract refers to observations made while conducting electron microscopy experiments. The section in the Experimental Procedures section detailing the electron microscopy experiments indicates that three separate compositions, not one complex, were in fact used; 1) adenovirus, 2) an EGF-horseradish peroxidase conjugate

(EGF-HRP) and 3) a colloidal gold-labeled anti-HRP antibody for binding and labeling EGF during electron microcopy. "For the cointernalization experiment with adenovirus, cells in the cold were incubated first with EGF-HRP for 1 hr, then washed and reincubated with adenovirus and gold-labeled anti-HRP for 4 hr." *Fitzgerald* at 616, top ¶ of first column. *See also Fitzgerald* at Figure 3, panel I (showing that adenovirus can be visualized alone and was not in association with colloidal gold labeled EGF in the cytosol). The use of the separate compositions in the electron microscopy experiments makes sense given that Fitzgerald's stated objective is to determine whether two separate entities, adenovirus and EFG, co-localize to the same intracellular compartment. "It was of interest, therefore, to determine whether adenovirus and EGF are located in the same organelles during internalization. To investigate this possibility, we carried out a cointernalization experiment with adenovirus and EGF." *Fitzgerald* at 608. If adenovirus and EGF were initially tethered together by colloidal gold it would be impossible to determine if they both independently co-localized in the same intracellular compartment. Therefore, Fitzgerald clearly did not contemplate the use of a construct where adenovirus and EGF are bound to colloidal gold as one would simply drag the other along for the ride, rendering the compositions utilized by Fitzgerald unsatisfactory for their intended purpose. Accordingly, this indicates that no suggestion or motivation for such a modification can be found in Fitzgerald or elsewhere in the prior art. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordan*, 733 F.2d 900 (Fed. Cir. 1984).

The Examiner further rejected claims 27 and 28 as being unpatentable over Fitzgerald in view of Lorberboum-Galiski *et al.* 85 PNAS 85 1922 (1988). As noted above Fitzgerald does not teach a gold complex comprising EGF and adenovirus bound to colloidal gold nor can there be any motivation to do so. Therefore, the Examiner's assertion that one of skill in the art would be motivated to replace Fitzgerald's EGF-PE with the IL-2-PE fusion protein of Lorberboum-Galiski is moot.

For at least the foregoing reasons, Applicants submit the grounds for rejecting claims 27 and 28 under 35 U.S.C. § 103(a) have been overcome and respectfully request they be withdrawn.

No Waiver

All of Applicants' arguments and amendments are without prejudice or disclaimer. Applicants submit that the independent claims are allowable over the documents of record, as discussed above. Applicants have not acquiesced to any such rejection and reserve the right to address the patentability of any additional claim features in the future.

CONCLUSION

Applicants submit the foregoing as a full and complete response to the Official Action dated February 15, 2011. Applicants submit that the amendments made herein and the remarks provided above do not present any new issues for review by the Examiner. If any issues exist that can be resolved with an Examiner's Amendment or a telephone conference, please contact Applicants' undersigned agent at 404.665.3099.

No additional fees are believed due, however the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment of fees to Deposit Account Number 50-5193.

Respectfully submitted,

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Attorney Docket No: CYT-0027